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A Reduced-Toxicity Regimen Is Associated with Durable Engraftment and Clinical Cure of Nonmalignant Genetic Diseases among Children Undergoing Blood and Marrow Transplantation with an HLA-Matched Related Donor

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A B S T R A C T

Blood and marrow transplantation (BMT) is a standard curative therapy for patients with nonmalignant genetic diseases. Myeloablative conditioning has been associated with significant regimen-related toxicity (RRT), whereas reduced-intensity conditioning regimens have been associated with graft failure. In this prospective pilot trial conducted at 2 centers between 2006 and 2013, we report the outcome of 22 patients with nonmalignant genetic diseases who were conditioned with a novel reduced-toxicity regimen: i.v. busulfan (16 mg/kg), alemtuzumab (52 mg/m^2), fludarabine (140 mg/m^2), and cyclophosphamide (105 mg/kg). The median age of the study population was 3.5 years (range, 5 months to 26 years). No cases of sinusoidal obstruction syndrome, severe or chronic graft-versus-host disease (GVHD), or primary graft failure were reported. Median time to neutrophil engraftment (>500 cells/μL) and platelet engraftment (>20K cells/μL) were 19 (range, 12 to 50) and 23.5 (range, 14 to 134) days, respectively. The median length of follow-up was 3 years (range, .2 to 6.3). The overall survival rates were 95% at 100 days (95% confidence interval, .72 to .99) and 90% at 6 years (95% confidence interval, .68 to .98). RRT and chronic GVHD are significant barriers to BMT for patients with nonmalignant genetic diseases. This alemtuzumab-based reduced-toxicity regimen appears to be promising with durable engraftment, effective cure of clinical disease, low rates of RRT, and no observed chronic GVHD.

INTRODUCTION

For many patients with nonmalignant genetic diseases, the decision burden regarding the immediate risks of blood and marrow transplantation (BMT) versus continuation of noncurative therapy often leads to delays in BMT. Unfortunately, many of these patients present for BMT after they have more advanced symptoms of their clinical disease, and such delays may be associated with poorer outcomes [1].

BMT with a histocompatible-related donor after standard myeloablative conditioning (MAC) has been associated with significant regimen-related toxicity (RRT) [2-5]. The nonmalignant genetic conditions represent a heterogeneous group of diseases with varying rates of RRT. These toxicities include noninfectious pulmonary toxicity and sinusoidal obstructive syndrome among patients with hemophagocytic lymphohistiocytosis, a high rate of grade ≥II graft-versus-host disease (GVHD) among patients with hemoglobinopathies, and a 9% graft failure rate among patients with thalassemia [6-8]. Interestingly, 30% of patients who received matched sibling donor BMT for Hurler syndrome developed mixed chimerism, despite the use of MAC, suggesting that sustained hematopoietic engraftment may pose a challenge among some metabolic disorders [9]. An

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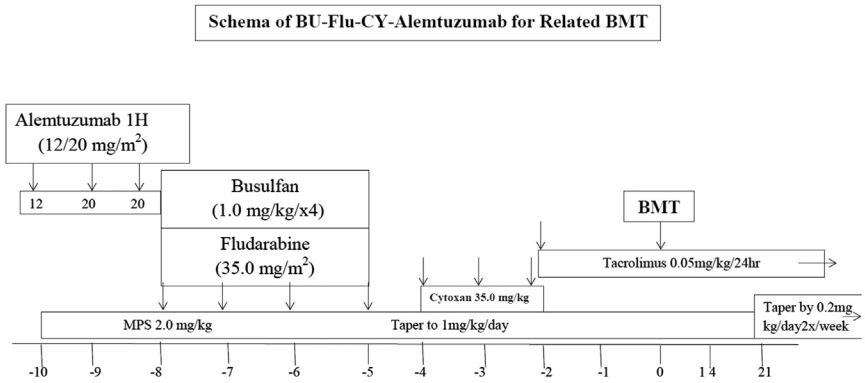

Figure 1. Schematic diagram of the treatment regimen. The conditioning regimen consisted of i.v. fludarabine (140 mg/m^2), i.v. busulfan (16 mg/kg; with pharmacokinetic dose adjustments to achieve overall target concentration steady state of 800 to 1000 ng/mL), alemtuzumab (52 mg/m^2), and cyclophosphamide (105 mg/kg). Either tacrolimus or cyclosporine was initiated on day −2 and continued for a minimum of 1 year post-transplant. Methylprednisolone (MPS) was tapered with a goal of discontinuation by day +35.

effective conditioning strategy for patients receiving related BMT for nonmalignant genetic diseases must be associated with low rates of RRT while remaining sufficiently immunoablative to allow for adequate levels of sustained donor chimerism.

Although RRT associated with standard MAC regimens (such as with busulfan, cyclophosphamide, and antithymocyte globulin [ATG]) may be acceptable for patients with leukemia whose disease may be immediately life threatening, this is a major obstacle to the application of curative BMT to nonmalignant genetic diseases. Reduction of the cyclophosphamide dose may expose patients to an increased risk of graft rejection, unless additional immunoablative drugs are added to the regimen. In 2004, Sodeni et al. [10] reported improved outcomes associated with dose reduction of cyclophosphamide and the addition of other agents to achieve adequate immunosuppression. Bernaudin et al. [11] showed that the addition of ATG to MAC regimens reduced the rejection rate among hematopoietic stem cell transplantation recipients with sickle cell disease from 22.6% to 3%. In the same year, we reported that the use of alemtuzumab (a monoclonal antibody that binds to CD52 on mature lymphocytes) was associated with reduced RRT, such as severe GVHD [12]. We hypothesized that among patients with nonmalignant genetic diseases receiving a matched related donor BMT, the addition of alemtuzumab to a regimen of busulfan, fludarabine, and a reduced dose of cyclophosphamide would maintain adequate immune suppression, allow acceptable rates of sustained donor engraftment, and allow low rates of RRT and chronic GVHD.

METHODS

This prospective pilot study was approved by the institutional review boards at Children's Hospital Los Angeles and Stanford Lucile Packard Children's Hospital. Informed consent was obtained in accordance with the Declaration of Helsinki.

Patients

Patients with nonmalignant genetic diseases who were candidates for allogeneic transplantation at either institution between 2006 and 2013 and had a 10/10 or 9/10 allele matched histocompatible sibling or related donor were eligible for this study protocol. Subjects must have had adequate physical and vital organ function, as measured by the following: (1) cardiac shortening fraction >26% or left ventricular ejection fraction at rest >40%; (2) bilirubin, alanine aminotransferase, and aspartate aminotransferase less than 3 times the upper limit of normal (as per local laboratory) for age (with the exception of isolated hyperbilirubinemia due to Gilbert syndrome); (3) serum creatinine less than 2 times the upper limit of normal for age or creatinine clearance or glomerular filtration rate >50% lower limit of normal for age; and (4) forced expiratory volume in 1 second, forced vital capacity, and diffusing capacity of lung for carbon monoxide (corrected for hemoglobin) >50% predicted or pulse oximetry oxygen saturation >92% on room air. Patients with Karnofsky performance status <70% or Lansky <40%; uncontrolled bacterial, viral, or fungal infections; seropositivity for HIV; acute active hepatitis; diagnosis of end-organ dysfunction; or diagnosis of severe combined immunodeficiency and Fanconi anemia were excluded.

Preparative Regimen

The conditioning regimen (Figure 1) consisted of i.v. fludarabine at a total dose of 140 mg/m^2, i.v. busulfan at a total dose of 1 mg/kg/dose for 16 doses (with pharmacokinetic dose adjustments after dose 1 and then doses 5 and 7 if adjustments were made) to achieve an overall target concentration steady state of 800 to 1000 ng/mL, alemtuzumab (Campath 1H, Genzyme Corporation, Cambridge, MA) at a total dose of 52 mg/m^2, and cyclophosphamide at a total dose of 105 mg/kg. Mesna was administered per standard operating procedure at each institution.

GVHD Prophylaxis

GVHD prophylaxis (Figure 1) consisted of a calcineurin inhibitor and methylprednisolone. Either tacrolimus or cyclosporine was initiated on day −2 and titrated to maintain a serum trough level of approximately 7 to 10 ng/dL for tacrolimus or 200 to 300 ng/dL for cyclosporine. The drug was continued for a minimum of 1 year post-transplant. Methylprednisolone was administered at 2 mg/kg/day in divided doses at the start of the conditioning regimen during the alemtuzumab infusion until day +3. Subsequently, methylprednisolone was tapered with a goal of discontinuation by day +35.

Graft Source

Histocompatible bone marrow donors 10/10 or 9/10 allele-matched were the main graft source on this protocol. One patient received a combination of umbilical cord and marrow products from the same related donor. The marrow was manipulated only for red blood cell or plasma removal per standard institutional practice in event of an ABO-mismatch between the donor and recipient.

Supportive Care

All patients remained hospitalized in protective isolation until there was evidence of engraftment of donor cells and sufficient clinical recovery. Viral prophylaxis consisted of i.v. acyclovir (1500 mg/m^2/day) until day +30 post-BMT. If the donor or recipient were positive for cytomegalovirus (CMV) serology, CMV PCR assays were sent at a minimum of weekly until day +100 post-BMT. If patients developed CMV viremia, ganciclovir (5 mg/kg) was administered intravenously twice daily. *Pneumocystis carinii* pneumonia prophylaxis consisted of oral trimethoprim-sulfamethoxazole 75 mg/m^2 or 2.5 mg/kg trimethoprim twice daily from admission until day −2 post-BMT. *Pneumocystis carinii* pneumonia prophylaxis was resumed after count recovery, per institutional practice. Standard antifungal prophylaxis consisted of fluconazole orally or intravenously 5 mg/kg until at least day +100 post-BMT. Standard antiseizure prophylaxis was administered. Patients with sickle cell disease continued antiseizure prophylaxis until discontinuation of calcineurin inhibitors.

Evaluations and Statistical Considerations

This was a prospective pilot study to evaluate the safety and efficacy of the proposed regimen among this patient population. A minimum of 20 patients were targeted for enrollment between 2006 and 2013. Stop criteria was established at a graft failure rate of more than 10% and/or an unexpected toxicity rate of more than 30%.

Neutrophil engraftment was defined as the first day of 3 consecutive days when the absolute neutrophil count exceeded 500/mm^3. Hematological recovery of donor origin was confirmed by short tandem repeat or fluorescent in situ hybridization. This analysis was repeated at 1 year post-BMT and if there was a concern regarding graft stability. Disease-specific observations such as enzymes levels or hemoglobin electrophoresis were routinely performed on days 100, 180, 270, and 360 after BMT. Platelet engraftment was defined as the first day of a minimum of 3 consecutive measurements on different days when the platelet count exceeded 20,000/mm^3 and the patient was platelet transfusion-independent for a minimum of 7 days. Time to T lymphocyte recovery was defined by the absolute number of donor-derived CD3$^+$ T lymphocytes >500/mm^3 and phytohemagglutinin response >25,000 CPM of tritiated thymidine incorporation. Time to antigen-specific T lymphocyte function was defined as a proliferate response to tetanus toxoid of greater than 3 times the background proliferation (stimulation index = 3).

To study pharmacokinetic clearance of alemtuzumab, levels were drawn on days 7, 14, 21, and 28 after BMT. Assays were performed as previously described [12]. No dose adjustments were made. Acute GVHD was assessed by the Glucksberg staging criteria [13]. Chronic GVHD was assessed by criteria of the National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic GVHD [14]. Overall survival of subjects was estimated using Kaplan-Meier analysis.

RESULTS

Patient Characteristics

As shown in Table 1, the study population was 68% female (n = 15), 41% Hispanic (n = 9), 23% black (n = 5), 23% white (n = 5), and 14% Asian (n = 3). The median age was 3.5 years (range, 5 months to 26 years). Pre-transplant diagnoses included sickle cell disease (n = 7), thalassemia (class I: n = 1; class II: n = 3), Hurler syndrome (n = 2), diamond blackfan anemia (n = 2), Kostmann syndrome (n = 2), Griscelli syndrome (n = 2), chronic granulomatous disease (n = 1), cartilage hair hypoplasia (n = 1), and Chediak-Higashi syndrome (n = 1).

Transplant Characteristics

The mean busulfan concentration steady state and area under the curve were 890 (±211) μg/L and 1285 (±387) μmol/L-min. Alemtuzumab levels were available for 11 patients at Children's Hospital Los Angeles. The median time to clearance of alemtuzumab was 14 days (range, 3 to 21 days). All patients received 10/10 related donor transplant. Two patients received 10/10 marrow donor transplants from a parent, and 1 patient received a combination of marrow and cord from a related sibling. The median total nucleated cell (TNC) count and CD34 dose was 4.6 × 10^8 cells/kg (range, 1.6 to 9.2 × 10^8) and 7.6 × 10^6 cells/kg (range, 2.4 to 23.3 × 10^6), respectively.

Engraftment/Immune Reconstitution

The median times to neutrophil engraftment (>500 cells/μL) and platelet engraftment (>20K cells/μL) were 19 (range, 12 to 50) and 23.5 (range, 14 to 134) days, respectively. All 22 patients achieved initial donor hematopoietic stem cell engraftment. Two patients required additional treatment post-BMT. One patient with thalassemia (UPN 4817) required a stem cell boost on day +83. Her mean busulfan level was 785 μg/L. Alemtuzumab levels were not performed for this patient. She received a TNC count and CD34 dose of 2.0 × 10^8 cells/kg and 2.8 × 10^6 cells/kg, respectively. She experienced poor count recovery associated with CMV viremia. Her initial chimerism on day 50 was 63% donor. However, after the stem cell boost she has remained ≥90% donor.

One patient with Hurler syndrome (UPN 3757) required 6 courses of donor lymphocyte infusions (DLIs). Her mean busulfan level was 920 μg/L. Alemtuzumab levels were not done for this patient. She received a TNC count and CD34 dose of 5.4 × 10^8 cells/kg and 7.2 × 10^6 cells/kg, respectively.

Table 1
Patient and Graft Characteristics and Outcomes

UPN	Diagnosis	Ethnicity	Age at BMT (yr)	CMV Status R/D	Sex Match R/D	ABO R/D	TNC (×10^8/kg)	CD34 (×10^6/kg)	ANC Engraftment Day Post-BMT	Platelet Engraftment Day Post-BMT	Last Follow-Up (yr)
3715	Hurler syndrome	Hispanic	1.8	−/−	F/F	O+/O+	4.3	7.7	19	22	4.5
3757	Hurler syndrome	White	1.2	−/−	F/M	A+/A+	5.4	7.2	31	54	6
3825	Diamond-blackfan anemia	Unspecified	26	−/−	F/F	A+/B+	4.7	4	13	22	4.1
997	Sickle cell disease	Hispanic	2.9	+/+	M/M	O+/O+	6.8	8.5	34	50	6
1002	Sickle cell disease	Black	14.2	−/+	M/F	A+/A+	3.7	2.4	18	80	1.8
1008	Kostmann syndrome	White	.6	−/+	M/F	A-B+	5.6	14.0	28	31	5.5
4096	Diamond-blackfan anemia	Hispanic	3.4	+/+	F/F	O−/O+	4.6	7.5	38	84	6.3
1033	Kostmann syndrome	Hispanic	6.4	+/+	F/M	B+/B+	3.5	6.3	16	23	5.1
1043	Chronic granulomatous disorder	Hispanic	9.3	−/−	M/F	A+/O+	6.4	6.6	15	94	4.9
1108	Sickle cell disease	Black	9.5	−/−	M/M	B+/O+	5.9	5.8	19	20	.8
1113	Hemoglobin H thalassemia	Asian	7.8	+/+	F/F	O+/B+	4.9	14.4	14	18	3.5
4631	Cartilage hair hypoplasia	White	2.3	+/−	F/M	O+/O+	1.1	.2	19	30	3.0
1127	Chediak-Higashi syndrome	White/Hispanic	1.6	−/+	F/M	AB+/A+	5.6	15.2	19	14	3.1
1151	Sickle cell disease	Hispanic	11.8	−/+	F/M	O+/O+	4.6	4.2	13	18	2.8
4817	Thalassemia	Middle Eastern	6.0	+/+	F/F	O−/A+	2.0	2.8	50	134	2.6
4970	Thalassemia	Asian	7.0	−/−	M/M	A+/A+	1.6	10.3	24	24	.5
1184	Sickle cell Anemia	Black	7.6	−/−	F/F	B+/A+	2.0	6.8	16	15	2.1
5034	Griscelli syndrome	Hispanic	.8	−/+	M/F	A+/A+	7.9	10.6	12	17	.2
1200	Griscelli Syndrome/ hemophagocytic lymphohistiocytosis	Hispanic	.4	−/−	F/M	O+/A+	9.2	13.4	19	25	2
5433	Sickle cell disease	Black	8.0	−/−	F/M	B+/B+	2.6	10.6	21	75	.8
5519	Thalassemia	Asian	2.0	−/+	F/M	B+/O+	6.4	23.3	14	19	.7
1299	Sickle cell anemia	Black	4.5	−/−	F/M	A+/A+	4.3	5.3	18	74	.7

R/D indicates recipient/donor; ANC, absolute neutrophil count.

Table 2
Hematopoietic Reconstitution

Hematopoietic Reconstitution	Median Time (days)
ANC engraftment (>500 cells/μL)	19 (range, 12-50)
Platelet engraftment (>20K cells/μL)	23.5 (range, 14-94)
Donor-derived $CD3^+$ T lymphocytes >500/mm^3	174 (range, 99-374)
Phytohemagglutinin response >25,000 CPM	169 (range, 97-316)
Antigen-specific T lymphocyte function	181 (range, 97-218)

Her initial chimerism on day 30 was 89% donor. Her CD3 donor percent ranged from 18% to 43% during her courses of DLI. At 6 years post-BMT she has stable donor engraftment with 58% CD3 and 66% whole blood donor chimerism.

Table 2 summarizes immune reconstitution data available for 11 patients at Children's Hospital Los Angeles. Median time to T lymphocyte recovery and phytohemagglutinin response >25,000 CPM was 174 (range, 99 to 374) and 169 (range, 97 to 316) days, respectively. Median time to antigen-specific T lymphocyte function was 181 days (range, 97 to 218).

RRT/Late Effects

There were no cases of grades III to IV acute or chronic GVHD. Ten patients developed grades I to II skin late-onset acute GVHD, and 1 patient developed grade II acute GVHD of the gut; the median time to onset of GVHD was 204 days. Sixteen patients have been followed in excess of 1 year and none has chronic GVHD.

There were no reported cases of sinusoidal obstructive syndrome. Median time to onset of infectious complications was 27 days (range, 6 to 282). Infectious complications included CMV viremia (n = 5), Epstein-Barr viremia (n = 1), mucormycosis (n = 1), and adenoviremia (n = 1). Two patients died: 1 patient with thalassemia died from interstitial pneumonitis on day +187 post-BMT (UPN 4970) and the other patient with Griscelli syndrome died from mucormycosis on day +67 post-BMT (UPN 5034). She had been maintained on standard prophylaxis when she was diagnosed. No late effects of BMT such as secondary malignancy, endocrine failures, and end-organ toxicities have been reported.

Overall and Disease-Free Survival

The median length of follow-up was 3 years (range, .2 to 6.3). Rates of overall survival were 95% at 100 days (95% confidence interval, .72 to .99) and 90% (95% confidence interval, .68 to .98) at 6 years. All patients (100%) have sustained predominant donor chimerism, with effective cure of their clinical disease and a Lansky/Karnofsky performance score of 100.

DISCUSSION

Nonablative regimens based on low-dose radiation (200 to 400 cGy) and fludarabine used to reduce RRT have been associated with poor rates of engraftment, especially among patients with hemoglobinopathies [15,16]. Lucarelli and Gaziev [17] reviewed the international experience in thalassemia and sickle cell disease and showed overall poor results and a reduced rate of sustained engraftment (only 1 in 11 transplants) with nonmyeloablative approaches [17]. A small cohort of adult patients with sickle cell disease (n = 11) conditioned with 300 cGy of total body irradiation and alemtuzumab showed promising results. Whether this regimen will have similar results among thalassemia patients remains to be seen [18]. With our current regimen, all patients with sickle cell disease (n = 7) achieved and sustained high-level donor chimerism (>99% donor). During the preparation of this article, Bhatia et al. [19] reported successful engraftment in a cohort of patients with sickle cell disease who received myeloablative busulfan and fludarabine and alemtuzumab but without cyclophosphamide before matched sibling donor transplant. Because patients with thalassemia and Hurler syndrome have historically been affected by higher rates of graft failure, we chose to judiciously de-escalate cyclophosphamide. The promising rates of engraftment associated with this regimen now raises the question as to whether further reductions in cyclophosphamide are possible and whether the current regimen can be successfully used in the unrelated donor setting.

Although the combination of myeloablative doses of busulfan and high doses of cyclophosphamide have been extensively used for immunocompetent patients with nonmalignant diseases, several studies have also shown the importance of some form of antibody-based lymphotoxic therapy (ATG, alemtuzumab) in the conditioning regimen. Bernaudin et al. [11] observed nonengraftment rates of 22.6% in patients with sickle cell disease who received busulfan and cyclophosphamide alone versus 2.9% in those who received busulfan, cyclophosphamide, and ATG as conditioning. Because lymphotoxic antibodies persist after stem cell infusion, they may both decrease the risk of GVHD but delay immune reconstitution. Either ATG or alemtuzumab has been shown to lower GVHD rates in a variety of transplant settings, including unrelated, mismatched, and nonmyeloablative transplants.

RRT is believed to be a major contributing factor to GVHD [19]. Therefore, conditioning regimens that cause less tissue injury may be associated with reduced rates of GVHD. Additionally, T cell depletion, such as occurs with the use of alemtuzumab, may be associated with reduced rates of GVHD [12,20-21]. Among patients with sickle cell disease undergoing sibling donor BMT with MAC, GVHD remains a significant complication [5,22].

In this current study, using an alemtuzumab-containing regimen, there were no cases of severe acute or extensive chronic GVHD. This is noteworthy, because there is no survival advantage to development of GVHD for patients with sublethal genetic diseases. It is interesting to note that the median time to onset of mild GVHD in this group was 204 days, with 8 patients experiencing mild late-onset acute GVHD. Such low rates of acute GVHD and no chronic GVHD offer promise for this regimen in the unrelated donor setting, which we are currently studying.

We previously reported that use of alemtuzumab as part of conditioning may be associated with a higher rate of viral infections without an increased rate of infectious-related mortality [12]. Indeed, although 20% of our patients did experience infectious morbidity, data available on the subset of patients who underwent BMT at Children's Hospital Los Angeles suggest this regimen is associated with prompt immune reconstitution. Among all patients, onset of infectious complications was primarily restricted to the first 30 days. Hence, appropriate measures to reduce infectious morbidity and mortality may be important in the early period after BMT for patients treated with this regimen.

Although the decrease in the dose of cyclophosphamide in this regimen was aimed primarily at reducing the early complications associated with MAC, it is possible the potentially dose-dependent late effects associated with cyclophosphamide, such as gonadal failure and secondary malignancies, may also be minimized with this regimen [23-25]. At a median of 3 years of follow-up, no late effects of BMT, such as

secondary malignancy, endocrine failures, and end-organ toxicities, have been observed. Further reduction or removal of cyclophosphamide from this regimen could be associated with improved outcomes by decreasing acute toxicity further. However, the risks of nonengraftment and/or need for DLI, especially among patients with hemoglobinopathies and/or Hurler syndrome, must be considered.

For patients with nonmalignant genetic diseases, early RRT, nonengraftment, and chronic GVHD may serve as potential barriers to successful BMT. This novel preparative regimen is promising, because it is associated with durable donor engraftment, 90% overall survival rate, low rates of early regimen-related complications (such as sinusoidal obstructive syndrome and acute GVHD), and no chronic GVHD. Longer follow-up is required to assess for a potential reduction in late effects associated with this regimen, such as gonadal failure and secondary malignancies.

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